Brief communication

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Association between HLA-A1 allele and schizophrenia gene(s) in patients refractory to conventional neuroleptics but responsive to clozapine medication

Key words:
chromosome 6; clozapine; HLA-A1; schizophrenia

Acknowledgments:
We thank Johan Westberg for critical review of the text and Heikki Katila for helpful comments. This study was supported by the Orion company, Espoo, Finland, the Sigrid Jusélius Foundation and the Academy of Finland.

Abstract: We report an association between HLA-A1 allele and a subgroup of schizophrenic patients refractory to conventional neuroleptic treatment but responsive to clozapine. The frequency of HLA-A1 was 58% among the schizophrenic patients not responding to conventional treatment but responsive to clozapine but only 10.5% among the patients responding to conventional neuroleptics. The HLA-A1 occurs in 20% of the random Finnish population. Our results indicate that HLA-A1 defines a subgroup of schizophrenic patients with a selective response to neuroleptics.

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Genetic susceptibility is believed to exist in schizophrenia, and various chromosomal regions are suggested to be involved. Genetic linkage between schizophrenia and chromosome 6 has been shown by several studies defining different genetic regions far apart from each other leaving the HLA region in between (1, 2). Also some HLA association studies have been performed (3–5) but with very diverse results. Diagnostic stringency is vital to HLA association studies. Like most diseases, schizophrenia is presumably heterogeneous, but subgrouping the patients according to the clinical criteria is difficult, and perhaps this is reflected in the results of the majority of studies. We wanted to perform an HLA association study on a particular patient group defined by the responsiveness to the therapy, thus representing a more homogeneous patient group.

The subjects were recruited from Finland-born patients referred to the Department of Psychiatry, Helsinki City Hospital, and they met DSM-III-R criteria for schizophrenia (6). The patients were categorized into two groups solely according to the criteria of Kane et al. (7) assessed by the Brief Psychiatric Rating Scale before the blood samples for HLA typing were taken (8). The first group, treatment resistant to conventional neuroleptic medication but responsive to clozapine, an atypical neuroleptic, comprised 19 patients (8 women and 11 men; mean age 36 (SD 9) years). The second group,

Received 2 May, revised,
accepted for publication 29 October 1997

Tissue Antigens. ISSN 0001-2815

Tissue Antigens 1998: 51: 200–203
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responsive to conventional neuroleptics consisted of 19 patients (10 women and 9 men; mean age 38 (SD 12) years). Finnish healthy blood donors (n=120) were used as controls. Stable doses of clozapine varied between 200 and 700 mg daily for a period of at least 4 weeks and of conventional neuroleptics between 157 and 1700 mg chlorpromazine equivalents, daily, for at least 4 weeks. By approval of the ethics committee, informed consent for the research procedure was given by all patients after the nature of the study had been fully explained.

HLA-A, B and DR typing of peripheral blood T and B cells was performed by lymphocytotoxicity method using commercial typing trays (3× 72-well trays) from Pel-Freez, Wisconsin, USA.

For comparison of proportions, two-sided Fisher's exact test was used. The P-values were adjusted for multiple comparisons and P-values<0.05 were considered statistically significant. The calculations were done with the program StatXact 3 for Windows (9). For difference of proportions, 99% confidence intervals were determined with the Confidence Interval Analysis program (10). The relative risk was estimated as recommended by Svejgaard (11).

The results are shown in Table 1. The distribution of HLA phenotypes of the schizophrenic patients as a group did not deviate from that of the random Finnish population. The patient group that was not responding to conventional neuroleptic treatment, however, differed significantly for one HLA allele compared to the other patients and to the controls. Of the nonresponder patient group, 58% had HLA-A1 while the patients responsive to conventional neuroleptics had it only in 10.5%. The difference is thus 37.9%, P=0.0011 (99% confidence interval 7.2–68.6%).

However, when the P-value is corrected with the number of comparisons made (2×29), it does not remain significant (P=0.064). The frequency of HLA-A1 is 20% among the Finnish normal population. No other statistically significant deviations or differences were observed in any of the three HLA loci analyzed. A slight increase was seen in the frequency of HLA-B8 allele but not in the frequency of HLA-DR3 allele. The HLA-A1, B8, DR3 haplotype is in high linkage disequilibrium and confers a well-known susceptibility to autoimmune diseases. While the HLA-A1 and B8 haplotypes were more often found among the clozapine-treated patients, the frequency was 0.157 as compared to 0.022 in the other patient group (P=0.025) and 0.066 among the Finns (haplotype frequencies not shown in Table 1). This increment did not, however, extend to the DR locus. The allele frequency of DR3 was the same in all three groups, and the HLA-A1, B8, DR3 extended haplotype frequency was lower than the A1, B8 haplotype frequency in the clozapine-treated group. Given that the HLA-A1 allele was found twice as often as HLA-B8 in the clozapine group, it indicates that the primary association is restricted to HLA-A1 rather than to that extended haplotype.

Distribution of HLA alleles among patients with schizophrenia responsive to treatment with conventional neuroleptics or refractory to conventional neuroleptics but responsive to clozapine

HLA allele	Conventional neuroleptics % (n=19)	Clozapine % (n=19)	Control[a] % (n=120)
A1	10.5	57.9[b] P=0.0011	20.1
A2	57.9	47.4	54.0
A3	57.9	42.1	44.4
A9	5.3	5.3	16.2
A10	15.8	5.3	7.8
A11	5.3	5.3	8.8
A19	10.5	15.8	19.6
A28	15.8	5.3 NS	11.3
B5	15.8	15.8	11.9
B7	42.1	21.1	24.3
B8	10.5 NS	31.6	20.0
B12	0	10.5	15.4
B13	0	5.3	6.0
B15	31.6	15.8	20.1
B16	10.5	10.5	9.3
B18	5.3	10.5	10.0
B22	5.3	5.3	5.0
B27	15.8	15.8	14.0
B35	26.3	26.3	27.2
B40	10.5	0	17.9
DR1	57.9	52.6 NS	35.6
DR2	31.6	21.1	23.5
DR3	26.3	26.3	22.6
DR4	26.3	21.1	28.7
DR5	5.3	5.3	11.0
DR6	26.3	26.3	23.2
DR7	5.3	10.5	12.3
DR8	10.5	5.3 NS	22.1
DR9	0	10.5	6.5

[a] Random Finnish population
[b] RR=11.6 when compared to conventionally treated group

Table 1

An association between HLA-A1 and schizophrenia has been reported, but other studies have been unable to confirm this connection (12–15). We could not find any altered frequency of HLA-A1 among schizophrenic patients in general but found a strong positive association between HLA-A1 and a subgroup of patients nonresponsive to conventional treatment.

Several recent studies (1, 2, 16, 17) have suggested that there

were susceptibility loci on chromosome 6 both telometric and centrometric to the HLA region. All these studies also support a model of locus heterogeneity, and the possibility could not be ruled out that one putative locus would be within the HLA region. The cause of schizophrenia is unknown. Theoretically it could be possible that viruses and their elimination via HLA-restricted immune response cross-reacting with neural tissue could play a causal role in some schizophrenics. It has been proposed that maternal influenza virus during prenatal life is one candidate for later schizophrenia of the fetus (18–22). As an example, conserved amino acid sequences have been found to be common to influenza A hemagglutinin and embryonic cadherins, which are essential to normal neurodevelopment. Influenza viruses however have not been shown to be restricted particularly to HLA-A1 allele.

On the other hand, our results do not exclude the possibility of linkage between HLA and schizophrenia susceptibility locus. Our patients with HLA-A1 may represent a subgroup of patients where HLA-A1 is in linkage disequilibrium with schizophrenia susceptibility locus telometric to HLA region similar to HLA-A3 and hemochromatosis (23). Thus, HLA-A1 could represent a useful marker for the further identification of the predisposing gene(s) on 6p.

Molecular genetic research in schizophrenia has been hampered by problems of the disease and its subtypes. As in the case of other common diseases such as diabetes mellitus, a number of possible genetic loci are likely to be involved in schizophrenia. Subdivision of patients for genetic studies is vital. Here we show that responsiveness to therapy is one way of subdividing the patients, and schizophrenia has a subgroup for which HLA association is found. The Finnish population is homogeneous and contains unique haplotypes (24). So, if the association described here is due to linkage to other susceptibility genes, the same association may not be found in other populations.

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